SPECIAL SESSION
ADVANCING AQUACULTURE DRUG APPROVALS BY
STRATEGIC COORDINATED RESEARCH

3RD MEETING OF THE
NATIONAL AQUACULTURE DRUG RESEARCH FORUM
August 03, 2006

Held in conjunction with the 12th Annual Drug Approval Coordination Workshop

MISSION STATEMENT

"To advance scientific knowledge and coordinate research activities
to expedite the approval of new animal drugs."

The goal of the forum is to develop a strategic plan component to work on issues relative to drug approval research activities, including (1) providing a forum for the exchange of information and mutual education between CVM review teams and representatives from academia, the pharmaceutical industry, aquaculture industry, and other government agencies, (2) establishing a repository of useful information and documents, and (3) to create a mechanism to broadly disseminate information relative to drug approval research activities.

Forum Co-Chairs:

FDA-OR	Renate Reimschuessel
USGS	Mark Gaikowski
USFWS	Jim Bowker
USDA-ARS	Dave Straus

Effective group structure includes the following:

- Group must be sustainable
- Group must have direction
- Those responsible must be accountable
- Group must establish monitoring program to evaluate progress
- Group must effectively and efficiently complete tasks

TECHNICAL PROJECT TEAMS

ENVIRONMENTAL RISK ASSESSMENT

Co-leaders: Charles Eirkson & Mark Gaikowski

TARGET ANIMAL SAFETY & EFFICACY

Co-leaders: Jim Bowker & Don Prater

ANALYTICAL METHODS VALIDATION

Co-leaders: Jeff Meinertz & James Nitao

ANTIMICROBIAL RESISTANCE

Co-leaders: Christine Moffitt & Steve Yan

EDUCATION AND OUTREACH

Co-leaders: Gary Jensen and Susan Storey
Participants: Tom Bell & Roy Yanong

General Discussion:

1. Decision making team; decision making process - The NADRF Co-Chairs agreed that the four Co-Chairs would form the decision making team (with respect to NADRF administrative-related matters) and that the decision making process would be by simple majority.

2. It was suggested by Don Prater that a 1 - 2 pg summary be drafted that describes how the group functions and procedures to use to post progress summaries.

3. Jim Bowker will update the Subject Matter Expert Directory

Update of Activities:

TARGET ANIMAL SAFETY & EFFICACY

Co-leaders: Don Prater & Jim Bowker

Participants: Matt Lucia, Niccole Wandelear, Maren Tuttle, Dave Petullo, Vaughn Ostland, Alan Johnson, Jim Powell, Ahmed Darwish, Jen Matysczak, Renate Reimschuessel, Susan Storey, Kathy Kilgore, Jeff Hill, Roy Yanong, and Molly Bowman

The group had previously decided to try to address one issue that might be readily achievable (i.e., how to deal with concomitant diseases during field efficacy trials) and one issue in which considerable effort (i.e., establishing disease models to minimize the number of pivotal field efficacy trials required to support a specific disease claim) will be required to adequately address. In addition, the group agreed to address another issue that should be readily resolved (drafting a document that clearly groups cold, cool, and warmwater fish species and identifies representative fish species within each group that may be considered when conducting efficacy and TAS studies).

CONCOMITANT DISEASES

Jim Bowker and Renate Reimschuessel met with Susan Storey to discuss how best to deal with concomitant diseases. In summary, presence of such pathogens will most likely jeopardize the acceptance of a pivotal field efficacy trial as pivotal. However, there are situations in which presence of such pathogens may not be considered "fatal." In such situations, adequate steps must be taken to (1) monitor and document the severity of secondary pathogens (primarily external parasites and bacteria), (2) provide a description of the pathogenesis is of the pathogen in the Final Study Report, and (3) provide a statement from the fish health specialist performing the fish health evaluation whether the severity of the infection directly contributed to mortality or negatively affected the outcome of the study. Jim will draft a points to consider document with respect to dealing with secondary pathogens, and will work with Renate (and Susan too) to finalize the document.

DISEASE MODELS

The issue with conducting field efficacy trials in which fish are "naturally infected" has been problematic due to biological and logistical challenges with respect to fish/pathogen cooperation and getting Investigators to the study site in a timely manner. CVM's Aquaculture Team is open to accepting results from efficacy trials in which a model was used to initiate the disease.

Acceptance of data from disease model trials will reduce the number of field efficacy trials required to complete technical sections for specific disease claims.

Discussion focused on (1) development of a disease model points to consider document, and (2) increase collaboration with respect to developing a model adequate for use in regulatory science. Ideally, one model will be developed and validated by researchers in different parts of the country. Several researchers are working somewhat independently on a columnaris model and results from their work will most likely be published in peer-reviewed journals. However, there was discussion relative to moving such a model from the academic realm to the regulatory arena. CVM's Aquaculture Team is encouraging increased collaboration with respect to method validation to ensure that the model is robust and works in the hands of Investigators in various parts of the country. As the group moves forward developing a model, thought should be given to developing a template to validate a disease model to facilitate drafting a Points to Consider Document.

A Points to Consider Document when designing and creating a disease model should include the following:

1. The mortality pattern (severity and rate) should mimic that of a natural infection
2. When to expose fish to the pathogen
3. How long to expose fish to the pathogen
4. Stress techniques used to exacerbate a disease outbreak
5. Equipment needed to induce a disease outbreak
6. Development of a robust model (how the model works on different species of fish by different Investigators)
7. Models must be validated (publish them!)
8. How to address proprietary issues (models developed by private industry and drug companies vs those developed in the public sector)
9. Work with smaller, more specific models (e.g., models specific to certain temperature class of fish)
10. Need for consistency and controls for each component of the study
11. Acceptable methods for each procedure (e.g., sedating, abrasions, stress)
12. Use of North American isolates within 3 years of culture of the isolate
13. Description of the proper techniques recommended for preserving isolate

Step 1. Develop a General Points to Consider Document when designing a Disease Model

Volunteers for this project include:

Renate Reimschuessel, Ahmed Darwish, Maren Tuttle, and Vaughn Ostland. We will ask Pat Gaunt if she is interested in participating. There was also a suggestion to contact Larry Hamell and Dave Spears (Canadian aquaculture vets)

Step 2. Develop Points to Consider Document specific for Columnaris

TEMPERATURE GROUPINGS

Define cold, cool and warm water fish groups (include tropical / ornamental fish)

1. Identify temperature ranges - One species can reside in more than one temperature grouping
2. Assemble list of fish species (representative species for each group)
3. Assemble list of commonly reared ornamental/tropical fish (what are the representative species). Do fish in this group fall within either the coolwater or warmwater group?
4. General information about what makes a cold, cool, warm or tropical fish

Articulate what this type of classification of fish will accomplish? Will this have regulatory impact?

This will be a general grouping for use, but will be used for review on a case-by-case basis. A lot depends on drug claim and use patterns.

This must be general and also be consistent from a fish culture standpoint.

Non-food fish (ornamentals) vs. food fish See Guidance on CVM's website

AADAP's Fish Database lists fish species cultured in the U.S. by the USFWS and State Natural Resource Agencies. It was recommend to use this database to begin to compile the list of commonly reared fish species in the U.S.

Points to Consider Document

Cold Cool Warm Ornamental Marine

Food vs. Non-food

Scaled vs. Non-scaled

Figure out a way to logically group fish that will help us go down the line towards a drug approval.
What are the technical section data requirements for ornamental fish (is human food safety data required?) What are representative species?

Ex.

Freshwater

Coldwater

Typically @ temperatures of x^{o}C to xx^{o}C

List all species of fish cultured in the U.S.

Pick Rainbow trout and 1 to 2 other fish from the list to fulfill label

Volunteers for this project include:

Roy Yanong, Jeff Hill, Kathy Kilgore, Jen Matysczak, Alan Johnson, and AADAP Representative

ANALYTICAL METHODS VALIDATION

Co-leaders: Jeff Meinertz & James Nitao

Participant: Jeff Meinertz

As you saw, my break out group was limited to 1 participant. Therefore, the analytical work group discussion went well. I remember giving a synopsis of the discussion to the general group, but I don't remember everything I said. I do remember saying something about the diversity of methods that could be applied to target animal safety, efficacy, environmental safety, and human food safety studies. I believe that each analytical method and its intended use can vary widely. Therefore, to generate one document that would cover all or even a portion of the parameters that can affect a method would be an enormous undertaking. I vaguely remember making the suggestion that the "expert list" should be more prominently displayed and when people run into issues concerning a particular subject, call the person on the list. As a professional favor, the person on the list should graciously assist the caller to remedy their issues. In reference to analytical methods, if someone needed an opinion on any aspect of developing or validating an analytical method for their particular use, they should simply call the people on the "expert list." To try to create a document of any other instructive material seems like an effort in futility.

Some ideas that came up for the analytical work group were to create a list of experts for the analytical group and briefly describe how we can serve aquaculture drug researchers. We can then periodically send out an e-mail asking participants if they have been approached with any issues and if the group, collectively could be of any assistance.

ANTIMICROBIAL RESISTANCE

Co-leaders: Steve Yan & Christine Moffitt
Participants: Tom Bell, Devona Weirich, Barbara Montwill, David Starling, Paul Rice, and Roz Schnick

Guidance for Industry #152 illustrates one example of a qualitative risk assessment. There have been several submissions to CVM that follow GFI #152, and the group discussed areas to focus on for future submissions, to improve the understanding of the risks of antimicrobial new animal drugs for aquaculture.

The following specific points about GFI #152 were covered in the discussions.

1. The drug's extent of use

This information is critical to the release assessment as well as for assisting in risk management strategies outlined in GFI #152. It includes drug usage patterns, quantity of usage, the scope and number of target animals treated at each farm, etc. Inclusion of this information can be very helpful for mitigating microbial food safety concerns.

2. Human consumption of food derived from aquatic species

The qualitative risk assessment includes *release*, *exposure* and *consequence* assessments. As an important component, information pertaining to exposure is important to facilitate the ultimate risk estimation. The group noted that in GFI #152 the *per capita* consumption data from USDA for seafood is grouped together under "fish and shellfish". In the case of specific drug applications, the conditions of use may be limited to one aquatic species. Therefore, a lump-sum exposure may not be relevant. The group felt that it will be helpful if consumption data are further broken down. Furthermore, the guidance matrix extrapolates using the estimated consumption of all wild captured fish and shellfish in the quantity consumed and imported products as well.

3. Other data gaps.

A process in which a sponsor or scientist identifies critical data gaps or ambiguous data will be of interest to regulators. Addressing these gaps through additional data gathering could resolve microbial food safety concerns. Where there are data gaps or ambiguous data, it will be helpful to add information from monitoring, or cross reference data already provided to FDA in other assessments for the same or similar conditions of use. To access and cross-reference data submitted by other sponsors, written permission from specific parties is required.

In other cases where data gaps cannot be filled, it may be necessary and sometimes easier to perform experimentation to supplement literature when the available literature can not directly address the relevant area of concern.

4. Sharing in a public forum

A suggestion was made during the discussions that authors of successful submissions on microbial food safety for antimicrobial new animal drug applications for aquaculture species

could facilitate successful future submissions by sharing their experiences on previous data submissions. Even with researchers working in the public sectors, such a discussion requires a prior agreement of those sponsors to permit sharing their expertise and experience. If permission for sharing is obtained, this sharing forum could be part of a future World Aquaculture Meeting such as that planned for San Antonio, TX, February, 2007. The forum could include sponsors, researchers, and CVM personnel, where participants could discuss strengths and weaknesses of submissions and how to improve and resolve data gaps. This proposal would be dependent upon travel budgets of involved parties, adequate interest and, particularly, permission from individual sponsors for sharing results.

ENVIRONMENTAL RISK ASSESSMENT

Co-leaders: Charles Eirkson & Mark Gaikowski (both absent)
Meeting chaired by: Eric Silberhorn, CVM **Attendees:** Not recorded

Eric Silberhorn reported on activities of the Center for Veterinary Medicine (CVM) in the past year related to risk assessment of veterinary drugs and aquaculture drugs in particular. These activities included the following:

1. Meetings with staff of the Environmental Protection Agency (EPA), Office of Water, to discuss the development of water quality benchmarks and associated labeling by CVM for use as risk mitigation measures in the approval of new aquaculture drugs.

2. Participation by Charles Eirkson and Eric Silberhorn in a Pellston Workshop sponsored by the Society of Environmental Toxicology and Chemistry (SETAC) on risk assessment of veterinary drugs. This workshop was held in Pensacola Beach, Florida in February, 2006. Charles Eirkson served on the steering committee for the workshop and Eric Silberhorn participated in the subgroup on aquatic exposure assessment. Workshop members are preparing chapters which will be incorporated into a SETAC book summarizing the state-of-the science in this area. Parts of the chapter on exposure assessment are expected to form the initial basis for future CVM guidance on the development of predicted environmental concentrations (PECs) for aquaculture drugs (see item below).

3. Continuing the development of methods for calculating predicted environmental concentrations (PECs) or environmental introduction concentrations (EICs) resulting from the use aquaculture drugs in various management systems (e.g., flow-through, pond, net pens). The methods will be used in environmental assessments to compare exposure levels with available toxicity data to determine whether there is potential for environmental effects to occur. CVM is currently preparing draft guidance for developing PECs and EICs and will seek input and comment on this guidance from the aquaculture community in the future.

Objective: Continue to develop guidance for methods for PEC calculations.

Discussions were held with participants to determine if the assumptions currently used exposure assessments for new aquaculture drugs are accurate and supportable.